Tipranavir disodium

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Drug Description

Tipranavir (TPV) is a sulfonamide-containing dihydropyrone. [1]

HIV/AIDS-Related Uses

TPV is a nonpeptidic protease inhibitor (NPPI) that has a uniquely robust resistance profile, demonstrating viral load responses against multiple protease inhibitor (PI) resistant HIV-1 strains both in vitro and in clinical studies.[2]

Ritonavir-boosted tipranavir (TPV/r) is currently being evaluated in treatment-experienced adult patients in Phase III clinical trials.[3] Pediatric formulations are currently being evaluated in HIV-infected patients age 2 to 18 years in Phase I, II, and III clinical trials. No results have been reported to date.[4] [5]

Pharmacology

TPV flexibly binds to the active site of HIV-1 protease, suppressing viral replication.[6] [7]

In a Phase II trial of TPV in PI-experienced patients, TPV/r (500/200 mg dose) consistently produced TPV trough plasma levels in excess of 10 times the IC90 (the concentration of drug required to inhibit viral replication by 90%) for PI-resistant HIV-1. Steady state plasma concentrations were reached within the first 7 days of treatment with twice-daily dosing.[8]

TPV/r demonstrated a greater than 10-fold reduction in viral load in treatment-experienced patients with multiple PI-resistant HIV.[9] In treatment-naive patients, TPV/r regimens demonstrated a 30-fold HIV RNA reduction after 2 weeks of treatment.[10]

A minimum of 16 to 20 protease gene mutations may be required for reduced susceptibility to TPV.[11] [12] Reduced susceptibility was demonstrated only in isolates with three or more universal protease-associated mutations (UPAMs) at codons L33I/V/F, V82A/F/L/T, I84V, and/or L90M, in addition to other protease gene mutations. Few isolates with only one or two UPAMs displayed reduced susceptibility to TPV; however, one or two of these mutations caused reduced susceptibility to available PIs. A breakpoint for TPV susceptibility was observed at an IC50 of approximately twofold wild type.[13]

TPV is a substrate and inducer of cytochrome P450 CYP3A in animals and humans. TPV/r acts as a CYP3A4 inhibitor due to the potent inhibitory effect of ritonavir.[14] In rats, glucuronidation of TPV is the major clearance mechanism.[15]

Adverse Events/Toxicity

The most common adverse events seen in TPV doses up to 1200 mg were mild to moderate nausea, vomiting, and diarrhea or loose stools. Adverse events were similar among all dosage regimens.[16] In a Phase II clinical trial of 216 patients, 15.3% experienced diarrhea of Grade 2 or greater, and 11.6% experienced vomiting; however, no clear dose response relationship was observed. A dose-dependent trend was observed for Grade 3 and 4 adverse events, laboratory abnormalities, and adverse event-related treatment discontinuations. Eleven patients (5.1%) experienced serious adverse events during the first 4 weeks of therapy; two were regarded as treatment-related.[17] In a phase II clinical trial of 296 patients on TPV/r alone or in combination with another PI, the frequency of adverse effects and laboratory abnormalities were similar between all arms after 4 weeks of therapy. Triglyceride elevations were the most frequent laboratory abnormality.[18]

Drug and Food Interactions

TPV decreases the steady state plasma concentrations of didanosine (ddI), stavudine, lamivudine, and zidovudine. However, the observed differences (15% to 46% decrease) in nucleoside reverse transcriptase inhibitor (NRTI) concentrations are not of clinical importance, and TPV can be combined with these agents.[19] Coadministration of TPV with enteric-coated (EC) ddI results in a 32% increase in TPV peak plasma concentration (Cmax) and a 34% decrease in TPV plasma trough concentration (C12h). EC ddI should be administered 4 hours apart from TPV/r.[20]

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Drug and Food Interactions (cont.)

Antacids reduce the absorption of TPV by 25% to 29%, requiring adjustment to the timing of antacid use. TPV increases atorvastatin plasma concentrations over ninefold, suggesting clinicians should carefully monitor patients on this combination for atorvastatin-associated adverse effects.[21]

Clinical Trials

For information on clinical trials that involve Tipranavir disodium, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Tipranavir disodium AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[22]

Dosage Form: Phase II clinical trials have evaluated TPV in a 300 mg hard-gel capsule. This formulation, which required high doses and a high pill burden to obtain optimal plasma levels, was replaced with a 250 mg soft-gel capsule available in a Self-Emulsifying Drug Delivery System.[23] [24] Phase II clinical trials have evaluated TPV/r at 500/100 mg, 500/200 mg, and 750/200 mg twice daily doses. Of these, the 500/200 mg dose has been selected for further study in Phase III trials based on optimal pharmacokinetic, safety, and tolerability data.[25] [26]

Storage: Store capsules at 2 C to 8 C in a cool, dry place protected from light, heat, and moisture. TPV may become less active in such conditions, and the soft-gel capsules may stick together in warm, moist conditions.[27]

Chemistry

CAS Name: 2-Pyridinesulfonamide, N-(3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl] phenyl)-5-(trifluoromethyl)-, disodium salt[28]

CAS Number: 191150-83-1[29]

Molecular formula: C31-H31-F3-N2-Na2-O5-S[30]

C 57.6%, H 4.8%, F 8.8%, N 4.3%, Na 7.1%, O 12.4%, S 5.0%[31]

Molecular weight: 646.64[32]

Other Names

PNU 140690E[33]

TPV[34]

PNU 140690[35]

Further Reading

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Manufacturer Information

Tipranavir disodium
Boehringer Ingelheim GmbH
55216 Ingelheim am Rehin
Germany

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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